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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/582,850	06/14/2006	Bertram Cezanne	MERCK-3185	6766

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EXAMINER	
JARRELL, NOBLE E	
ART UNIT	PAPER NUMBER
1624	
MAIL DATE	DELIVERY MODE
05/21/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/582,850	CEZANNE ET AL.	
	Examiner	Art Unit	
	Noble Jarrell	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 March 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-37* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/14/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of group I in the reply filed on 3/28/2008 is acknowledged. The traversal is on the ground(s) that all of the compounds share a common core. This is not found persuasive because when fairly considered, there is not seen a significant common core for compounds of groups I-XI. In group I, a combination of variables Z, Z', and E form a piperidine ring. In group II, a combination of variables Z, Z', and E form a piperazine ring. In addition, each of these groups differs by variable T. Variable T is piperidine in group I and phenyl in group II. A search for these two groups cannot be considered co-extensive.

The requirement is still deemed proper and is therefore made FINAL.

Specification

2. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The current title describes a small portion of formula I. It fails to take into account the presence of a bipiperidinyl group.

Information Disclosure Statement

3. The information disclosure statement filed 6/14/2006 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each cited foreign patent document; each non-patent literature publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. It has been placed in the application file, but the information referred to therein has not been considered.

Claim Objections

4. Claims 1-37 objected to because of the following informalities: non-elected subject matter exists within these claims. In addition, claim 30 appears to missing a word or phrase after the phrase "wherein E is". Appropriate correction is required.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-37 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a salt or stereoisomer of formula I, does not reasonably provide enablement for a solvate of formula I. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. Applicants are enabled for preparation of a salt or diastereomers of formula I, but are not enabled for preparation of any solvate of formula I.

> The factors to be considered in determining whether a disclosure meets the enablement requirements of 35 U.S.C. 112, first paragraph, have been described in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir., 1988). The court in Wands states, "Enablement is not precluded by the necessity for some experimentation, such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue', not 'experimentation'" (*Wands*, 8 USPQ2sd 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations" (*Wands*, 8 USPQ2d 1404). Among these factors are: (1) the nature of the invention; (2) the breadth of the claims; (3) the state of the prior art; (4) the predictability or unpredictability of the art; (5) the relative skill of those in the art; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

Consideration of the relevant factors sufficient to establish a *prima facie* case for lack of enablement is set forth herein below:

(1) The nature of the invention and (2) the breadth of the claims:

The claims are drawn to compounds with a core structure of a C(O)-bipiperidinyl group connected to a chain containing 4 different variables and compositions containing the same.

(3) The state of the prior art and (4) the predictability or unpredictability of the art:

Vippagunta et al. (*Advanced Drug Delivery Reviews*, **2001**, *48*, 3-26) teach that solvate formation is unpredictable within a series of related molecules because each compound responds uniquely to solvate formation (page 18, section 3.4).

(5) The relative skill of those in the art:

One of ordinary skill in the art can replicate a synthetic procedure as depicted in scheme 1 of the specification (pages 37-38).

(6) The amount of direction or guidance presented and (7) the presence or absence of working examples:

The specification has provided guidance for preparation of a salt or stereoisomer of formula I.

However, the specification does not provide guidance for preparation of any solvate of formula I.

(8) The quantity of experimentation necessary:

Considering the state of the art as discussed by the references above, particularly with regards to claims 1-37 and the high unpredictability in the art as evidenced therein, and the lack of guidance provided in the specification, one of ordinary skill in the art would be burdened with undue experimentation to practice the invention commensurate in the scope of the claims.

7. Claims 24 and 27-29 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for *in vitro* inhibition of factors Xa and VIIa and the treatment of thromboses, does not reasonably provide enablement for all disorders related to inhibition of factors VIIa and Xa. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. Applicants are enabled for the *in vitro* binding of prepared compounds to factor VIIa and Xa receptors and the relationship of inhibition of these two receptors to treatment of thrombosis. Applicants are not enabled for the *in vitro* use of prepared compounds as well as all of the disorders listed in claim 27.

> The factors to be considered in determining whether a disclosure meets the enablement requirements of 35 U.S.C. 112, first paragraph, have been described in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir., 1988). The court in Wands states, "Enablement is not precluded by the necessity for some experimentation, such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue', not 'experimentation'" (*Wands*, 8 USPQ2sd 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations" (*Wands*, 8 USPQ2d 1404). Among these factors are: (1) the nature of the invention; (2) the breadth of the claims; (3) the state of the prior art; (4) the predictability or unpredictability of the art; (5) the relative skill of those in the art; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

Consideration of the relevant factors sufficient to establish a *prima facie* case for lack of enablement is set forth herein below:

(1) The nature of the invention and (2) the breadth of the claims:

The claims are drawn to inhibition of factor VIIa and Xa with a compound of formula I and compositions containing the same.

(3) The state of the prior art and (4) the predictability or unpredictability of the art:

Turpie (*Expert Opinion in Pharmacotherapy*, **2004**, *5(6)*, 1373-84) teaches that inhibition of factor Xa is related to antithrombotic therapy. Kher (*Expert Opinion in Investigational Drugs*, **2001**, *10(12)*, 2175-83) teaches that inhibition of factor VIIa is related to antithrombotic treatment as well.

(5) The relative skill of those in the art:

One of ordinary skill in the art can determine the affinity of prepared compounds in the instant application to factor VIIa and Xa receptors (table on page 44).

(6) The amount of direction or guidance presented and (7) the presence or absence of working examples:

The specification has provided guidance for guidance for *in vitro* binding of prepared compounds to factor VIIa and Xa receptors. In addition, applicants are enabled for the cause and effect of inhibition of factor VIIa or Xa with antithrombotic therapy.

However, the specification does not provide guidance that these compounds can work *in vitro* even though *in vitro* testing data is provided.

(8) The quantity of experimentation necessary:

The pharmaceutical art has been known for its unpredictability due to various conflicting pathways, or biological factors that are sometimes genetically unique to individuals. In the instant case, it is shown that compounds 1, 2, 5, and 49 bind to factor VIIa and Xa receptors *in vitro*. See *Hoffman v. Klaus* 9 USPQ 2d 1657, and *Ex Parte Powers* 220 USPQ 925 regarding types of testing needed to support *in vivo* uses.

Considering the state of the art as discussed by the references above, particularly with regards to claims 24 and 27-29 and the high unpredictability in the art as evidenced therein, and the lack of guidance provided in the specification, one of ordinary skill in the art would be

burdened with undue experimentation to practice the invention commensurate in the scope of the claims.

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 1-37 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicants do not give any guidance as to what the phrase "pharmaceutically acceptable derivatives" refers to. A "pharmaceutically acceptable derivative" could be a prodrug or metabolite, for example. Because this phrase is unclear in scope, every claim which depends on claim 1 is rendered indefinite as well. In claim 27, what type of cancer is being treated? Cancer is more than 100 different diseases ("Cancer definition", http://www.medterms.com/script/main/art.asp?articlekey=2580, accessed November 27, 2007).

Conclusion

10. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Noble Jarrell whose telephone number is (571) 272-9077. The examiner can normally be reached on M-F 7:30 A.M - 6:00 P.M. EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. James O. Wilson can be reached on (571) 272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Noble Jarrell/
Examiner, Art Unit 1624

/James O. Wilson/
Supervisory Patent Examiner, Art Unit 1624